

# **BOTOX COSMETIC- botulinum toxin type a injection, powder, lyophilized, for solution** **Allergan, Inc.**

## **HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use BOTOX<sup>®</sup> Cosmetic safely and effectively.

See full prescribing information for BOTOX Cosmetic.

**BOTOX Cosmetic (onabotulinumtoxinA) for injection,  
for intramuscular use**

**Initial U.S. Approval: 1989**

### **WARNING: DISTANT SPREAD OF TOXIN EFFECT**

*See full prescribing information for complete boxed warning.*

The effects of BOTOX Cosmetic and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults, particularly in those patients who have an underlying condition that would predispose them to these symptoms. (5.2)

### **RECENT MAJOR CHANGES**

- Warnings and Precautions, Serious Adverse Reactions with Unapproved Use (5.3)

08/2015

### **INDICATIONS AND USAGE**

BOTOX Cosmetic is an acetylcholine release inhibitor and a neuromuscular blocking agent indicated for:

- Temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients (1.1)
- Temporary improvement in the appearance of moderate to severe lateral canthal lines associated with orbicularis oculi activity in adult patients (1.2)

### **DOSAGE AND ADMINISTRATION**

- Glabellar Lines Administration: 0.1 mL (4 Units) by intramuscular injection into each of 5 sites, for a total dose of 20 Units (2.3)
- Lateral Canthal Lines Administration: 0.1 mL (4 Units) into each of 3 sites per side (6 total injection points), for a total of 24 Units (2.3)
- Dosage and administration recommendations should be followed; In treating adults for more than one approved indications with BOTOX and BOTOX Cosmetic, do not exceed a total dose of 360 Units administered in a 3 month interval (2.1)
- See Preparation and Dilution Technique for instructions on BOTOX Cosmetic reconstitution, storage, and preparation before injection (2.2)

### **DOSAGE FORMS AND STRENGTHS**

For Injection: 50 Units or 100 Units vacuum-dried powder in a single-use vial for reconstitution (3)

### **CONTRAINDICATIONS**

- Hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation (4.1, 5.4)
- Infection at the injection site (4.2)

### **WARNINGS AND PRECAUTIONS**

- Potency Units of BOTOX Cosmetic are not interchangeable with other preparations of botulinum toxin products (5.1, 11)
- Spread of toxin effects; swallowing and breathing difficulties can lead to death. Seek immediate medical attention if respiratory, speech or swallowing difficulties occur (5.2, 5.7)
- Potential serious adverse reactions after BOTOX injections for unapproved uses (5.3)
- Adverse event reports have been received involving the cardiovascular system, some with fatal outcomes. Use caution when administering to patients with pre-existing cardiovascular disease. (5.5)
- Concomitant neuromuscular disorder may exacerbate clinical effects of treatment (5.6)

- Use with caution in patients with compromised respiratory function or dysphagia (5.7)

#### -----ADVERSE REACTIONS-----

The most common adverse reactions are (6.1):

- Glabellar Lines: eyelid ptosis (3%)
- Lateral Canthal Lines: eyelid edema (1%)

**To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-433-8871 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

#### -----DRUG INTERACTIONS-----

Patients receiving concomitant treatment of BOTOX Cosmetic and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like agents), or muscle relaxants, should be observed closely because the effect of BOTOX Cosmetic may be potentiated (7)

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**

**Revised: 8/2015**

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## **FULL PRESCRIBING INFORMATION**

### **WARNING: DISTANT SPREAD OF TOXIN EFFECT**

Postmarketing reports indicate that the effects of BOTOX Cosmetic and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and upper limb spasticity and at lower doses. *[See Warnings and Precautions (5.2)]*

## **1 INDICATIONS AND USAGE**

### **1.1 Glabellar Lines**

BOTOX Cosmetic (onabotulinumtoxinA) for injection is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.

### **1.2 Lateral Canthal Lines**

BOTOX Cosmetic is indicated for the temporary improvement in the appearance of moderate to severe lateral canthal lines associated with orbicularis oculi activity in adult patients.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Instructions for Use

The potency Units of BOTOX Cosmetic (onabotulinumtoxinA) for injection are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX Cosmetic cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method [see Description (11)].

Indication specific dosage and administration recommendations should be followed. In treating adult patients for one or more indications with BOTOX and BOTOX Cosmetic, the maximum cumulative dose should generally not exceed 360 Units, in a 3 month interval.

The safe and effective use of BOTOX Cosmetic depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques. Physicians administering BOTOX Cosmetic must understand the relevant neuromuscular and structural anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures and disease, especially when injecting near the lungs.

### 2.2 Preparation and Dilution Technique

BOTOX Cosmetic is supplied in single-use 50 Units and 100 Units per vial. Prior to intramuscular injection, reconstitute each vacuum-dried vial of BOTOX Cosmetic with sterile, preservative-free 0.9% Sodium Chloride Injection USP. Draw up the proper amount of diluent in the appropriate size needle and syringe to obtain a reconstituted solution at a concentration of 4 Units/0.1 mL and a total treatment dose of 20 Units in 0.5 mL for glabellar lines and 24 Units in 0.6 mL for lateral canthal lines (see Table 1). Then slowly inject the diluent into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Gently mix BOTOX Cosmetic with the saline by rotating the vial. Record the date and time of reconstitution on the space on the label. BOTOX Cosmetic should be administered within 24 hours after reconstitution. During this time period, reconstituted BOTOX Cosmetic should be stored in a refrigerator (2° to 8°C). BOTOX Cosmetic vials are for single-use only. Discard any remaining solution.

**Table 1: Dilution Instructions for BOTOX Cosmetic Vials (100 Units and 50 Units)**

<b>Diluent* Added to 100 Unit Vial</b>	<b>Resulting Dose Units per 0.1 mL</b>	<b>Diluent* Added to 50 Unit Vial</b>	<b>Resulting Dose Units per 0.1 mL</b>
2.5 mL	4 Units	1.25 mL	4 Units

\*Preservative-free 0.9% Sodium Chloride Injection, USP Only

Reconstituted BOTOX Cosmetic should be clear, colorless, and free of particulate matter. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and whenever the solution and the container permit. Do not freeze reconstituted BOTOX Cosmetic.

### 2.3 Administration

Draw at least 0.5 mL (for glabellar lines) or 0.6 mL (for lateral canthal lines) of the properly reconstituted toxin into the sterile syringe, preferably a tuberculin syringe and expel any air bubbles in the syringe barrel. Remove the needle used to reconstitute the product and attach a 30-33 gauge needle. Confirm the patency of the needle.

#### *Glabellar Lines*

Glabellar facial lines arise from the activity of the corrugator and orbicularis oculi muscles. These muscles move the brow medially, and the procerus and depressor supercilii pull the brow inferiorly.

This creates a frown or “furrowed brow”. The location, size, and use of the muscles vary markedly among individuals. Lines induced by facial expression occur perpendicular to the direction of action of contracting facial muscles. An effective dose for facial lines is determined by gross observation of the patient's ability to activate the superficial muscles injected.

In order to reduce the complication of ptosis the following steps should be taken:

- Avoid injection near the levator palpebrae superioris, particularly in patients with larger brow depressor complexes.
- Lateral corrugator injections should be placed at least 1 cm above the bony supraorbital ridge.
- Ensure the injected volume/dose is accurate and where feasible kept to a minimum.
- Do not inject toxin closer than 1 cm above the central eyebrow.

Inject 4 Units/0.1 mL of reconstituted BOTOX Cosmetic intramuscularly into each of 5 sites, 2 in each corrugator muscle and 1 in the procerus muscle for a total dose of 20 Units (see Figure 1). Typically the initial doses of reconstituted BOTOX Cosmetic induce chemical denervation of the injected muscles one to two days after injection, increasing in intensity during the first week.

The duration of effect of BOTOX Cosmetic for glabellar lines is approximately 3-4 months. The safety and effectiveness of dosing with BOTOX Cosmetic more frequently than every 3 months have not been clinically evaluated.

**Figure 1:**



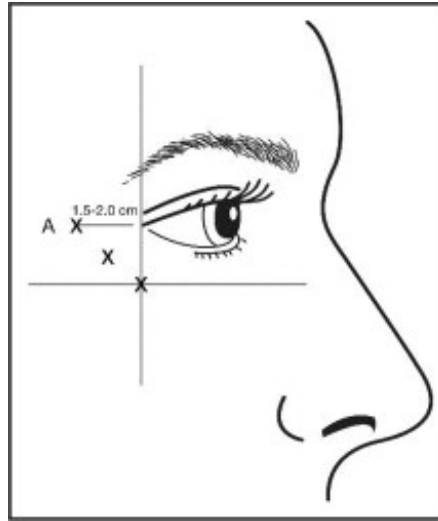
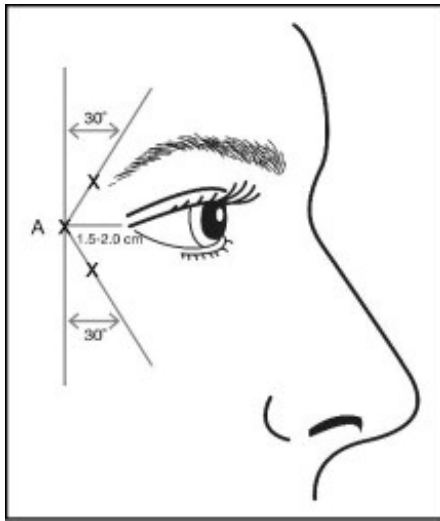
### *Lateral Canthal Lines*

Lateral canthal lines arise largely from the activity of the orbicularis oculi muscles around the eye responsible for blinking and eyelid closure. Forceful contraction of the orbicularis oculi results in lateral and radially oriented folds (crow's feet lines) which originate from the lateral canthus. The distribution of these radial lines differs among patients.

Injections should be given with the needle bevel tip up and oriented away from the eye. Inject 4 Units/0.1 mL of reconstituted BOTOX Cosmetic into 3 sites per side (6 total injection points) in the lateral orbicularis oculi muscle for a total of 24 Units/0.6 mL (12 Units per side). The first injection (A) should be approximately 1.5-2.0 cm temporal to the lateral canthus and just temporal to the orbital rim. If the lines in the lateral canthal region are above and below the lateral canthus, inject per Figure 2. Alternatively, if the lines in the lateral canthal region are primarily below the lateral canthus, inject per Figure 3.

**Figure 2:**

**Figure 3:**



For simultaneous treatment with glabellar lines, the dose is 24 Units for lateral canthal lines and 20 Units for glabellar lines (see Glabellar Lines Administration and Figure 1), with a total dose of 44 Units.

The safety and effectiveness of dosing with BOTOX Cosmetic more frequently than every 3 months have not been clinically evaluated.

### 3 DOSAGE FORMS AND STRENGTHS

- For injection: 50 Units, vacuum-dried powder in a single-use vial for reconstitution
- For injection: 100 Units, vacuum-dried powder in a single-use vial for reconstitution

### 4 CONTRAINDICATIONS

#### 4.1 Known Hypersensitivity to Botulinum Toxin

BOTOX Cosmetic is contraindicated in individuals with known hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation [see Warnings and Precautions (5.4)].

#### 4.2 Infection at the Injection Site(s)

BOTOX Cosmetic is contraindicated in the presence of infection at the proposed injection site(s).

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Lack of Interchangeability between Botulinum Toxin Products

**The potency Units of BOTOX Cosmetic are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX Cosmetic cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method [see Description (11)].**

#### 5.2 Spread of Toxin Effect

Postmarketing safety data from BOTOX Cosmetic and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death

related to spread of toxin effects. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, and particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, symptoms consistent with spread of toxin effect have been reported at doses comparable to or lower than doses used to treat cervical dystonia and upper limb spasticity. Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders occur.

No definitive serious adverse event reports of distant spread of toxin effect associated with dermatologic use of BOTOX/BOTOX Cosmetic at the labeled dose of 20 Units (for glabellar lines), 24 Units (for lateral canthal lines), 44 Units (for simultaneous treatment of lateral canthal lines and glabellar lines), or 100 Units (for severe primary axillary hyperhidrosis) have been reported.

No definitive serious adverse event reports of distant spread of toxin effect associated with BOTOX for blepharospasm at the recommended dose (30 Units and below), strabismus, or chronic migraine at the labeled doses have been reported.

### **5.3 Serious Adverse Reactions with Unapproved Use**

Serious adverse reactions, including excessive weakness, dysphagia, and aspiration pneumonia, with some adverse reactions associated with fatal outcomes, have been reported in patients who received BOTOX injections for unapproved uses. In these cases, the adverse reactions were not necessarily related to distant spread of toxin, but may have resulted from the administration of BOTOX to the site of injection and/or adjacent structures. In several of the cases, patients had pre-existing dysphagia or other significant disabilities. There is insufficient information to identify factors associated with an increased risk for adverse reactions associated with the unapproved uses of BOTOX. The safety and effectiveness of BOTOX for unapproved uses have not been established.

### **5.4 Hypersensitivity Reactions**

Serious and/or immediate hypersensitivity reactions have been reported. These reactions include anaphylaxis, serum sickness, urticaria, soft tissue edema, and dyspnea. If such a reaction occurs, further injection of BOTOX Cosmetic should be discontinued and appropriate medical therapy immediately instituted. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent, and consequently the causal agent cannot be reliably determined.

### **5.5 Cardiovascular System**

There have been reports following administration of BOTOX of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease. Use caution when administering to patients with pre-existing cardiovascular disease.

### **5.6 Pre-Existing Neuromuscular Disorders**

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia and respiratory compromise from onabotulinumtoxinA [see *Warnings and Precautions* (5.7)].

### **5.7 Dysphagia and Breathing Difficulties**

Treatment with BOTOX and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or oropharyngeal muscles that control swallowing or

breathing. *[see Warnings and Precautions (5.2)]*.

Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several months, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised.

Treatment with botulinum toxins may weaken neck muscles that serve as accessory muscles of ventilation. This may result in a critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been postmarketing reports of serious breathing difficulties, including respiratory failure.

Patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscle for the treatment of cervical dystonia have been reported to be at greater risk for dysphagia. Limiting the dose injected into the sternocleidomastoid muscle may reduce the occurrence of dysphagia. Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.

Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin *[see Warnings and Precautions (5.2)]*.

### **5.8 Pre-existing Conditions at the Injection Site**

Caution should be used when BOTOX Cosmetic treatment is used in the presence of inflammation at the proposed injection site(s), ptosis, or when excessive weakness or atrophy is present in the targeted muscle(s).

### **5.9 Corneal Exposure and Ulceration in Patients Treated with BOTOX for Blepharospasm**

Reduced blinking from BOTOX Cosmetic injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect, and corneal ulceration, especially in patients with VII nerve disorders. Vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

### **5.10 Spatial Disorientation, Double Vision or Past-pointing in Patients Treated for Strabismus**

Inducing paralysis in one or more extraocular muscles may produce spatial disorientation, double vision or past pointing. Covering the affected eye may alleviate these symptoms.

### **5.11 Human Albumin and Transmission of Viral Diseases**

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is also considered extremely remote. No cases of transmission of viral diseases or CJD have ever been reported for albumin.

## **6 ADVERSE REACTIONS**

The following adverse reactions to BOTOX Cosmetic (onabotulinumtoxinA) for injection are discussed in greater detail in other sections of the labeling:

- Spread of Toxin Effects *[see Warnings and Precautions (5.2)]*
- Hypersensitivity *[see Contraindications (4.1) and Warnings and Precautions (5.4)]*
- Dysphagia and Breathing Difficulties *[see Warnings and Precautions (5.7)]*

### **6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates



observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

BOTOX and BOTOX Cosmetic contain the same active ingredient in the same formulation, but have different labeled Indications and Usage. Therefore, adverse events observed with the use of BOTOX also have the potential to be observed with the use of BOTOX Cosmetic.

In general, adverse reactions occur within the first week following injection of BOTOX Cosmetic and while generally transient, may have a duration of several months or longer. Localized pain, infection, inflammation, tenderness, swelling, erythema, and/or bleeding/bruising may be associated with the injection. Needle-related pain and/or anxiety may result in vasovagal responses (including e.g., syncope, hypotension), which may require appropriate medical therapy.

Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of nearby muscles may also occur due to spread of toxin [see *Warnings and Precautions* (5.2)].

#### *Glabellar Lines*

Table 2 lists selected adverse reactions reported by  $\geq 1\%$  of BOTOX Cosmetic treated subjects (N=405) aged 18 to 75 who were evaluated in the randomized, placebo-controlled clinical studies to assess the use of BOTOX Cosmetic in the improvement of the appearance of glabellar lines.

**Table 2: Adverse Reactions Reported by  $\geq 1\%$  of the BOTOX Cosmetic treated Patients and More Frequent than in Placebo-treated Patients in Double-blind, Placebo-controlled Clinical Studies of Treatment of Glabellar Lines**

Adverse Reactions by System Organ Class	BOTOX Cosmetic (N=405)	Placebo (N=130)
General Disorders and Administration Site Conditions		
Facial pain	6 (1%)	0 (0%)
Nervous System Disorders		
Facial paresis	5 (1%)	0 (0%)
Eye Disorders		
Eyelid ptosis	13 (3%)	0 (0%)
Musculoskeletal and Connective Tissue Disorders		
Muscular Weakness	6 (1%)	0 (0%)

#### *Lateral Canthal Lines*

Table 3 lists selected adverse reactions reported within 90 days following injection by  $\geq 1\%$  of BOTOX Cosmetic treated subjects (N=526) aged 18 to 75 who were evaluated in two randomized, double-blind, placebo-controlled clinical studies to assess the use of **BOTOX Cosmetic** in the improvement of the appearance of lateral canthal lines alone.

**Table 3: Adverse Reaction Reported by  $\geq 1\%$  of BOTOX Cosmetic treated Patients and More Frequent than in Placebo-treated Patients Within 90 Days, in Double-blind, Placebo-controlled Clinical Studies of Treatment of Lateral Canthal Lines**

Adverse Reactions by System Organ Class	BOTOX Cosmetic Units (N=526)	Placebo (N=530)
Eye disorders		
Eyelid edema	5 (1%)	0 (0%)

## 6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Treatment with botulinum toxins may result in the formation of neutralizing antibodies that may reduce the effectiveness of subsequent treatments by inactivating biological activity of the toxin.

In three Lateral Canthal Line trials, 916 subjects (517 subjects at 24 Units and 399 subjects at 44 Units) treated with BOTOX Cosmetic had specimens analyzed for antibody formation. Among the 916 BOTOX Cosmetic treated subjects, 14 subjects (1.5%) developed binding antibodies and no subjects (0%) developed the presence of neutralizing antibodies.

The data reflect the subjects whose test results were considered positive or negative for neutralizing activity to BOTOX Cosmetic in a mouse protection assay. The results of these tests are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to BOTOX Cosmetic with the incidence of antibodies to other products may be misleading.

The critical factors for neutralizing antibody formation have not been well characterized. The results from some studies suggest that botulinum toxin injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation. The potential for antibody formation may be minimized by injecting with the lowest effective dose given at the longest feasible intervals between injections.

## 6.3 Post-marketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin *[see Warnings and Precautions (5.4, 5.7)]*.

There have also been reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease.

New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events.

The following adverse reactions by System Organ Class have been identified during post-approval use of BOTOX/BOTOX Cosmetic:

### **Ear and labyrinth disorders**

Hypoacusis; tinnitus; vertigo

### **Eye disorders**

Diplopia; strabismus; visual disturbances; vision blurred

### **Gastrointestinal disorders**

Abdominal pain; diarrhea; dry mouth; nausea; vomiting

### **General disorders and administration site conditions**

Denervation; malaise; pyrexia

### **Metabolism and nutrition disorders**

Anorexia

## **Musculoskeletal and connective tissue disorders**

Muscle atrophy; myalgia

## **Nervous system disorders**

Brachial plexopathy; dysarthria; facial palsy; hypoaesthesia; localized numbness; myasthenia gravis; paresthesia; peripheral neuropathy; radiculopathy; syncope

## **Respiratory, thoracic and mediastinal disorders**

Aspiration pneumonia; dyspnea; respiratory depression and/or respiratory failure

## **Skin and subcutaneous tissue disorders**

Alopecia, including madarosis; hyperhidrosis; pruritus; skin rash (including erythema multiforme, dermatitis psoriasiform, and psoriasiform eruption)

## **7 DRUG INTERACTIONS**

No formal drug interaction studies have been conducted with BOTOX Cosmetic (onabotulinumtoxinA) for injection.

### **7.1 Aminoglycosides and Other Agents Interfering with Neuromuscular Transmission**

Co-administration of BOTOX Cosmetic and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated.

### **7.2 Anticholinergic Drugs**

Use of anticholinergic drugs after administration of BOTOX Cosmetic may potentiate systemic anticholinergic effects.

### **7.3 Other Botulinum Neurotoxin Products**

The effect of administering different botulinum neurotoxin products at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

### **7.4 Muscle Relaxants**

Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of BOTOX Cosmetic.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

Teratogenic Effects: Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. BOTOX Cosmetic should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When BOTOX Cosmetic (4, 8, or 16 Units/kg) was administered intramuscularly to pregnant mice or rats two times during the period of organogenesis (on gestation days 5 and 13), reductions in fetal body weight and decreased fetal skeletal ossification were observed at the two highest doses. The no-effect dose for developmental toxicity in these studies (4 Units/kg) is approximately 5 times the average high human dose for glabellar lines and lateral canthal lines of 44 Units on a body weight basis (Units/kg).

When BOTOX Cosmetic was administered intramuscularly to pregnant rats (0.125, 0.25, 0.5, 1, 4, or 8 Units/kg) or rabbits (0.063, 0.125, 0.25, or 0.5 Units/kg) daily during the period of organogenesis (total of 12 doses in rats, 13 doses in rabbits), reduced fetal body weights and decreased fetal skeletal ossification were observed at the two highest doses in rats and at the highest dose in rabbits. These doses were also associated with significant maternal toxicity, including abortions, early deliveries, and maternal death. The developmental no-effect doses in these studies of 1 Unit/kg in rats is approximately 1.4 times the average human dose based on Units/kg, and the developmental no-effect dose of 0.25 Units/kg in rabbits is less than the average high human dose based on Units/kg.

When pregnant rats received single intramuscular injections (1, 4, or 16 Units/kg) at three different periods of development (prior to implantation, implantation, or organogenesis), no adverse effects on fetal development were observed. The developmental no-effect level for a single maternal dose in rats (16 Units/kg) is approximately 22 times the average high human dose based on Units/kg.

### **8.3 Nursing Mothers**

It is not known whether BOTOX Cosmetic is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BOTOX Cosmetic is administered to a nursing woman.

### **8.4 Pediatric Use**

Safety and effectiveness in patients below the age of 18 years have not been established.

### **8.5 Geriatric Use**

#### *Glabellar Lines*

In the two initial glabellar lines clinical studies of BOTOX Cosmetic, the responder rates appeared to be higher for subjects younger than age 65 than for subjects 65 years or older [see *Clinical Studies (14)*].

#### *Lateral Canthal Lines*

In the two lateral canthal lines clinical studies of BOTOX Cosmetic, the responder rates appeared to be higher for subjects younger than age 65 than for subjects 65 years or older.

## **10 OVERDOSAGE**

Excessive doses of BOTOX Cosmetic (onabotulinumtoxinA) for injection may be expected to produce neuromuscular weakness with a variety of symptoms.

Symptoms of overdose are likely not to be present immediately following injection. Should accidental injection or oral ingestion occur or overdose be suspected, these patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalization. The person should be medically supervised for several weeks for signs and symptoms of systemic muscular weakness which could be local, or distant from the site of injection [see *Boxed Warning and Warnings and Precautions (5.2, 5.7)*].

If the musculature of the oropharynx and esophagus are affected, aspiration may occur which may lead to development of aspiration pneumonia. If the respiratory muscles become paralyzed or sufficiently weakened, intubation and assisted respiration may be necessary until recovery takes place. Supportive care could involve the need for a tracheostomy and/or prolonged mechanical ventilation, in addition to other general supportive care.

In the event of overdose, antitoxin raised against botulinum toxin is available from the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. However, the antitoxin will not reverse any botulinum toxin-induced effects already apparent by the time of antitoxin administration. In the event of suspected or actual cases of botulinum toxin poisoning, please contact your local or state Health Department to process a request for antitoxin through the CDC. If you do not receive a response within 30 minutes, please contact the CDC directly at 1-770-488-7100. More information can be obtained at

## **11 DESCRIPTION**

BOTOX Cosmetic (onabotulinumtoxinA) for injection, is a sterile, vacuum-dried purified botulinum toxin type A, produced from fermentation of Hall strain *Clostridium botulinum* type A intended for intramuscular use. It is purified from the culture solution by dialysis and a series of acid precipitations to a complex consisting of the neurotoxin, and several accessory proteins. The complex is dissolved in sterile sodium chloride solution containing Albumin Human and is sterile filtered (0.2 microns) prior to filling and vacuum-drying.

The primary release procedure for BOTOX Cosmetic uses a cell-based potency assay to determine the potency relative to a reference standard. The assay is specific to Allergan's products BOTOX and BOTOX Cosmetic. One Unit of BOTOX Cosmetic corresponds to the calculated median intraperitoneal lethal dose (LD<sub>50</sub>) in mice. Due to specific details of this assay such as the vehicle, dilution scheme and laboratory protocols, Units of biological activity of BOTOX Cosmetic cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method. The specific activity of BOTOX Cosmetic is approximately 20 Units/nanogram of neurotoxin complex.

Each vial of BOTOX Cosmetic contains either 50 Units of *Clostridium botulinum* type A neurotoxin complex, 0.25 mg of Albumin Human, and 0.45 mg of sodium chloride; or 100 Units of *Clostridium botulinum* type A neurotoxin complex, 0.5 mg of Albumin Human, and 0.9 mg of sodium chloride in a sterile, vacuum-dried form without a preservative.

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

BOTOX Cosmetic blocks neuromuscular transmission by binding to acceptor sites on motor nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a pre-synaptic protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings. When injected intramuscularly at therapeutic doses, BOTOX Cosmetic produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. In addition, the muscle may atrophy, axonal sprouting may occur, and extrajunctional acetylcholine receptors may develop. There is evidence that reinnervation of the muscle may occur, thus slowly reversing muscle denervation produced by BOTOX Cosmetic.

### **12.2 Pharmacodynamics**

No formal pharmacodynamic studies have been conducted with BOTOX Cosmetic (onabotulinumtoxinA) for injection.

### **12.3 Pharmacokinetics**

Using currently available analytical technology, it is not possible to detect BOTOX Cosmetic in the peripheral blood following intramuscular injection at the recommended doses.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### *Carcinogenesis*

Long term studies in animals have not been performed to evaluate carcinogenic potential of BOTOX Cosmetic.

## Mutagenesis

BOTOX Cosmetic was negative in a battery of *in vitro* (microbial reverse mutation assay, mammalian cell mutation assay, and chromosomal aberration assay) and *in vivo* (micronucleus assay) genetic toxicologic assays.

## Impairment of Fertility

In fertility studies of BOTOX Cosmetic (4, 8, or 16 Units/kg) in which either male or female rats were injected intramuscularly prior to mating and on the day of mating (3 doses, 2 weeks apart for males, 2 doses, 2 weeks apart for females) to untreated animals, reduced fertility was observed in males at the intermediate and high doses and in females at the high dose. The no-effect doses for reproductive toxicity (4 Units/kg in males, 8 Units/kg in females) are approximately 5-10 times the average high human dose for glabellar lines and lateral canthal lines of 44 Units on a body weight basis (Units/kg).

## 14 CLINICAL STUDIES

### 14.1 Glabellar Lines

Two phase 3 randomized, multi-center, double-blind, placebo-controlled trials of identical design were conducted to evaluate BOTOX Cosmetic for use in the temporary improvement of the appearance of moderate to severe glabellar facial lines. The trials enrolled healthy adults (ages 18 to 75) with glabellar lines of at least moderate severity at maximum frown. Subjects were excluded if they had ptosis, deep dermal scarring, or an inability to substantially lessen glabellar lines even by physically spreading them apart. Subjects received a single treatment with BOTOX Cosmetic (N=405, combined trials) or placebo (N=132, combined trials). Injection volume was 0.1 mL/injection site, for a dose/injection site in the active treatment groups of 4 Units. Subjects were injected intramuscularly in five sites, 1 in the procerus muscle and 2 in each corrugator supercilii muscle, for a total dose in the active treatment groups of 20 Units.

The co-primary efficacy endpoints were the investigator's rating of glabellar line severity at maximum frown and the subject's global assessment of change in appearance of glabellar lines, both at Day 30 post-injection. For the investigator rating, using a 4-point grading scale (0=none, 3=severe) a responder was defined as having a severity grade of 0 or 1. For the subject's global assessment of change, the ratings were from +4 (complete improvement) to -4 (very marked worsening). A responder was defined as having a grade of at least +2 (moderate improvement). After completion of the randomized studies, subjects were offered participation in an open label, repeat treatment study to assess the safety of repeated treatment sessions.

The combined results of these two efficacy trials are presented here. The mean age was 46 years, with 32 subjects (6%) ≥65 years of age. Most of the subjects were women (82%), and Caucasian (84%). At baseline, 210 subjects (39%) had glabellar line severity scores at rest of moderate or severe.

In these trials, the severity of glabellar lines was reduced for up to 120 days in the BOTOX Cosmetic group compared to the placebo group as measured both by investigator rating of glabellar line severity at maximum frown (Table 4), and by subject's global assessment of change in appearance of glabellar lines (Table 5).

**Table 4: Investigator's Assessment of Glabellar Line Severity at Maximum Frown – Responder Rates (% and Number of Subjects with Severity of None or Mild)**

Day	BOTOX Cosmetic	Placebo	Difference <sup>a</sup>
7	74% 299/405	6% 8/132	68% (62, 74)
30 <sup>b</sup>	80%	3%	77%

	325/405	4/132	(72, 82)
60	70% 283/403	2% 2/130	69% (64, 74)
90	48% 192/403	2% 3/128	45% (40, 51)
120	25% 102/403	2% 2/128	24% (19, 29)

<sup>a</sup> 95% confidence intervals are shown in parenthesis

<sup>b</sup> Day 30: Co-Primary Efficacy Time point, p<0.001

**Table 5: Subject's Assessment of Change in Appearance of Glabellar Lines – Responder Rates (% and Number of Subjects with at Least Moderate Improvement)**

Day	BOTOX Cosmetic	Placebo	Difference <sup>a</sup>
7	82% 334/405	9% 12/132	73% (68, 80)
30 <sup>b</sup>	89% 362/405	7% 9/132	83% (77, 88)
60	82% 330/403	4% 5/130	78% (73, 83)
90	63% 254/403	3% 4/128	60% (54, 66)
120	39% 157/403	1% 1/128	38% (33, 43)

<sup>a</sup> 95% confidence intervals are shown in parenthesis

<sup>b</sup> Day 30: Co-Primary Efficacy Time point, p<0.001

In the subset of subjects with resting severity scores of moderate or severe, the investigator assessment of a resting severity of mild or none at Day 30 was also achieved by more BOTOX Cosmetic treated subjects (74%, 119/161) than placebo treated subjects (20%, 10/49).

Analysis of the limited number of subjects 65 years or older suggested a lower treatment-associated response compared to subjects less than 65 years of age (Table 6).

**Table 6: Investigator's and Subject's Assessment – Responder Rates for Subjects <65 and ≥65 Years of Age at Day 30**

Assessment	Age Group	BOTOX Cosmetic (N=405)	Placebo (N=132)	Difference <sup>a</sup>
Investigators (maximal frown)	<65	83% 316/382	2% 2/123	81% (77, 86)
Subjects	<65	91% 346/382	7% 8/123	84% (79, 90)
Investigators (maximal frown)	≥65	39% 9/23	22% 2/9	17% (-17, 51)
Subjects	≥65	70% 16/23	11% 1/9	58% (31, 86)

<sup>a</sup> 95% confidence intervals are shown in parenthesis

Exploratory analyses by gender suggested that responder rates in the BOTOX Cosmetic treated group

were higher for women than for men for both the investigator assessment (Day 30; 85% of 334 women, 59% of 71 men) and the Subject Assessment (Day 30; 93% of women, 72% of men). In the limited number of non-Caucasian subjects (n=64 in the BOTOX Cosmetic treated group) the responder rates were similar to those observed in the Caucasian subjects.

## 14.2 Lateral Canthal Lines

Two multicenter, randomized, double-blind, placebo-controlled trials evaluated BOTOX Cosmetic (N=833, randomized to receive any BOTOX Cosmetic treatment or N=529 randomized to receive placebo) for the temporary improvement in the appearance of moderate to severe lateral canthal lines (LCL). Study 1 assessed BOTOX Cosmetic treatment of LCL alone; Study 2 also assessed simultaneous treatment of LCL and glabellar lines (GL). Both trials enrolled healthy adults with moderate to severe LCL at maximum smile at baseline; Study 2 also required subjects to have moderate to severe GL at maximum frown at baseline.

In the 5-month Study 1, subjects were randomized to receive a single blinded treatment of 24 Units/0.6 mL (12 Units per side) consisting of 4 Units/0.1 mL into 3 sites of each orbicularis oculi muscle with either BOTOX Cosmetic (N=222) or placebo (N=223).

In the 7-month Study 2, subjects were randomized to receive either BOTOX Cosmetic in the LCL region and placebo in the GL region (24 Units; N=306), or BOTOX Cosmetic in the LCL and GL regions (44 Units [24 Units for LCL and 20 Units for GL]; N=305), or placebo in the LCL and GL regions (0 Units; N=306). Subjects received the same 24 Units regimen for LCL as in Study 1, and the labeled 20 Units (5 injections, 4 Units per site) for GL. Subjects received the same treatment at days 1 and 120.

The primary efficacy measure was the assessment of LCL severity at maximum smile using the 4-point Facial Wrinkle Scale with Photnumeric Guide (FWS; 0=none, 1= mild, 2=moderate, 3=severe). The FWS assessment was performed independently by both investigators and subjects. The primary timepoint was day 30 following the first treatment, as compared to baseline.

The primary efficacy response definition used for the pivotal trials was a composite  $\geq 2$ -grade improvement from baseline in LCL severity at maximum smile, assessed by both investigator and subject on a per-subject basis. For Studies 1 and 2, the proportion of responders was statistically significant favoring BOTOX Cosmetic (24 Units [LCL alone] and 44 Units [LCL and GL]) compared to placebo at day 30 (Table 7).

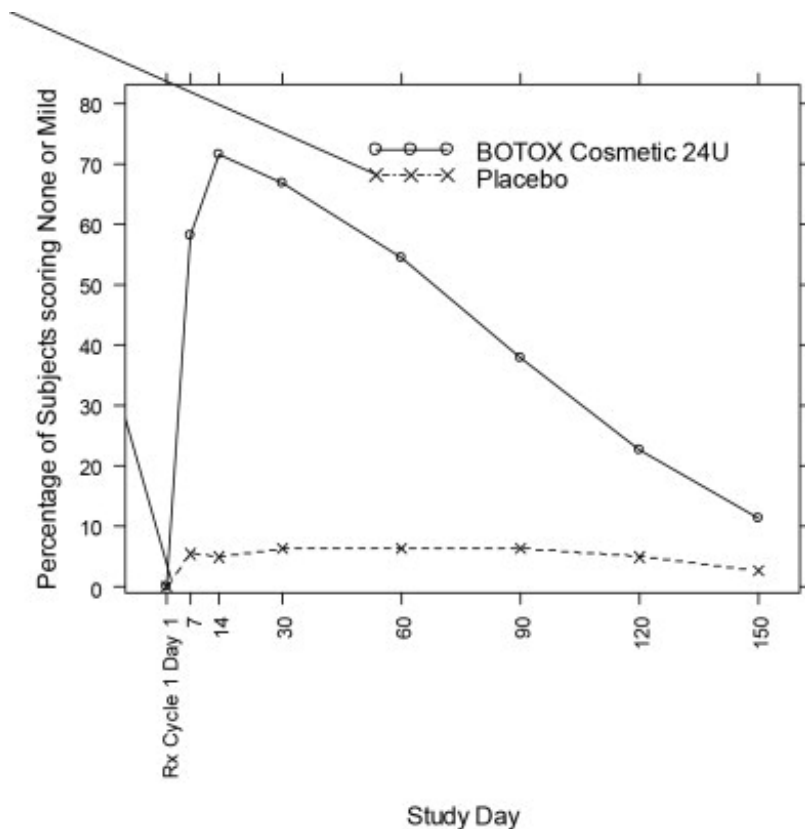
**Table 7: Studies 1 and 2: Composite Investigator and Subject Assessment of LCL at Maximum Smile at Day 30 – Responder Rates (% and Number of Subjects Achieving  $\geq 2$ -Grade Improvement from Baseline)**

Study	BOTOX Cosmetic 24 Units	BOTOX Cosmetic 24 Units LCL and 20 Units GL	Placebo
Study 1	26.1% 58/222	-	1.3% 3/223
Study 2	20.3% 62/306	21.3% 65/305	0.0% 0/306

The secondary endpoint of a responder defined as achieving a grade of none or mild for Study 1 as measured by the investigator is presented in Figure 4 below.

**Figure 4. Percentage of Subjects with Treatment Success (% of Subjects achieving None or Mild from Baseline) by Visit (Study 1)**





## 16 HOW SUPPLIED/STORAGE AND HANDLING

**BOTOX Cosmetic** is supplied in a single-use vial in the following sizes:

50 Units: NDC 0023-3919-50

100 Units: NDC 0023-9232-01

The top and bottom flaps of the BOTOX Cosmetic cartons have a tamper-evident seal that contains a translucent silver Allergan logo. Vials of BOTOX Cosmetic have a holographic film on the vial label that contains the name “Allergan” within horizontal lines of rainbow color. In order to see the hologram, rotate the vial back and forth between your fingers under a desk lamp or fluorescent light source. (Note: the holographic film on the label is absent in the date/lot area.) Each BOTOX Cosmetic vial label and carton also contains the U.S. License number: 1145.

Do not use the product and contact Allergan for additional information at 1-800-890-4345 from 7:00 AM to 3:00 PM Pacific Time if:

- the horizontal lines of rainbow color or the name “Allergan” are not present on the vial label
- the tamper-evident seal is not intact and present on both ends of the carton
- the translucent silver Allergan logo on the seal is not clearly visible or has a black circle with a diagonal line through it (i.e., prohibition sign)
- the U.S. License number 1145 is not present on the vial label and carton

### Storage

Unopened vials of BOTOX Cosmetic should be stored in a refrigerator 2° to 8°C (36° to 46°F). Do not use after the expiration date on the vial. Reconstituted BOTOX Cosmetic should be stored in a refrigerator 2° to 8°C (36° to 46°F) and administered within 24 hours.

## 17 PATIENT COUNSELING INFORMATION

**See FDA-approved patient labeling (Medication Guide)**

Provide a copy of the Medication Guide and review the contents with the patient.

### **17.1 Swallowing, Speaking or Breathing Difficulties, or Other Unusual Symptoms**

Patients should be advised to inform their doctor or pharmacist if they develop any unusual symptoms (including difficulty with swallowing, speaking, or breathing), or if any existing symptom worsens [see *Boxed Warning and Warnings and Precautions (5.2, 5.7)*].

### **17.2 Ability to Operate Machinery or Vehicles**

Patients should be counseled that if loss of strength, muscle weakness, blurred vision, or drooping eyelids occur, they should avoid driving a car or engaging in other potentially hazardous activities.

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Irvine, CA 92612

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## **MEDICATION GUIDE**

**BOTOX®**

**BOTOX® Cosmetic (Boe-tox)**

**(onabotulinumtoxinA)**

**for Injection**

Read the Medication Guide that comes with **BOTOX** or **BOTOX Cosmetic** before you start using it and each time it is given to you. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. You should share this information with your family members and caregivers.

**What is the most important information I should know about BOTOX and BOTOX Cosmetic?**

**BOTOX and BOTOX Cosmetic may cause serious side effects that can be life threatening, including:**

- **Problems breathing or swallowing**
- **Spread of toxin effects**

**These problems can happen hours, days, to weeks after an injection of BOTOX or BOTOX Cosmetic. Call your doctor or get medical help right away if you have any of these problems after treatment with BOTOX or BOTOX Cosmetic:**

**1. Problems swallowing, speaking, or breathing. These problems can happen hours, days, to weeks after an injection of BOTOX or BOTOX Cosmetic** usually because the muscles that you use to breathe and swallow can become weak after the injection. Death can happen as a complication if you have severe problems with swallowing or breathing after treatment with **BOTOX** or **BOTOX Cosmetic**.

- People with certain breathing problems may need to use muscles in their neck to help them breathe. These people may be at greater risk for serious breathing problems with **BOTOX** or **BOTOX Cosmetic**.
- Swallowing problems may last for several months. People who cannot swallow well may need a feeding tube to receive food and water. If swallowing problems are severe, food or liquids may go into your lungs. People who already have swallowing or breathing problems before receiving **BOTOX** or **BOTOX Cosmetic** have the highest risk of getting these problems.

**2. Spread of toxin effects.** In some cases, the effect of botulinum toxin may affect areas of the body away from the injection site and cause symptoms of a serious condition called botulism. The symptoms of botulism include:

- loss of strength and muscle weakness all over the body
- double vision
- blurred vision and drooping eyelids
- hoarseness or change or loss of voice (dysphonia)
- trouble saying words clearly (dysarthria)
- loss of bladder control
- trouble breathing
- trouble swallowing

These symptoms can happen hours, days, to weeks after you receive an injection of **BOTOX** or **BOTOX Cosmetic**.

These problems could make it unsafe for you to drive a car or do other dangerous activities. See "What should I avoid while receiving **BOTOX** or **BOTOX Cosmetic**?"

There has not been a confirmed serious case of spread of toxin effect away from the injection site when **BOTOX** has been used at the recommended dose to treat chronic migraine, severe underarm sweating, blepharospasm, or strabismus, or when **BOTOX Cosmetic** has been used at the recommended dose to treat frown lines and/or crow's feet lines.

### **What are BOTOX and BOTOX Cosmetic?**

**BOTOX** is a prescription medicine that is injected into muscles and used:

- to treat overactive bladder symptoms such as a strong need to urinate with leaking or wetting accidents (urge urinary incontinence), a strong need to urinate right away (urgency), and urinating often (frequency) in adults when another type of medicine (anticholinergic) does not work well enough or cannot be taken.
- to treat leakage of urine (incontinence) in adults with overactive bladder due to neurologic disease when another type of medicine (anticholinergic) does not work well enough or cannot be taken.
- to prevent headaches in adults with chronic migraine who have 15 or more days each month with headache lasting 4 or more hours each day.
- to treat increased muscle stiffness in elbow, wrist, and finger muscles in adults with upper limb spasticity.
- to treat the abnormal head position and neck pain that happens with cervical dystonia (CD) in adults.
- to treat certain types of eye muscle problems (strabismus) or abnormal spasm of the eyelids (blepharospasm) in people 12 years and older.

**BOTOX** is also injected into the skin to treat the symptoms of severe underarm sweating (severe primary axillary hyperhidrosis) when medicines used on the skin (topical) do not work well enough.

**BOTOX Cosmetic** is a prescription medicine that is injected into muscles and used to improve the look of moderate to severe frown lines between the eyebrows (glabellar lines) in adults for a short period of time (temporary).

**BOTOX Cosmetic** is a prescription medicine that is injected into the area around the side of the eyes to improve the look of crow's feet lines in adults for a short period of time (temporary).

You may receive treatment for frown lines and crow's feet lines at the same time.

It is not known whether **BOTOX** is safe or effective in people younger than:

- 18 years of age for treatment of urinary incontinence
- 18 years of age for treatment of chronic migraine
- 18 years of age for treatment of spasticity

- 16 years of age for treatment of cervical dystonia
- 18 years of age for treatment of hyperhidrosis
- 12 years of age for treatment of strabismus or blepharospasm

**BOTOX Cosmetic** is not recommended for use in children younger than 18 years of age.

It is not known whether **BOTOX** and **BOTOX Cosmetic** are safe or effective to prevent headaches in people with migraine who have 14 or fewer headache days each month (episodic migraine).

It is not known whether **BOTOX** and **BOTOX Cosmetic** are safe or effective for other types of muscle spasms or for severe sweating anywhere other than your armpits.

### **Who should not take BOTOX or BOTOX Cosmetic?**

Do not take **BOTOX** or **BOTOX Cosmetic** if you:

- are allergic to any of the ingredients in **BOTOX** or **BOTOX Cosmetic**. See the end of this Medication Guide for a list of ingredients in **BOTOX** and **BOTOX Cosmetic**.
- had an allergic reaction to any other botulinum toxin product such as *Myobloc*<sup>®</sup>, *Dysport*<sup>®</sup>, or *Xeomin*<sup>®</sup>
- have a skin infection at the planned injection site
- are being treated for urinary incontinence and have a urinary tract infection (UTI)
- are being treated for urinary incontinence and find that you cannot empty your bladder on your own (only applies to people who are not routinely catheterizing)

### **What should I tell my doctor before taking BOTOX or BOTOX Cosmetic?**

**Tell your doctor about all your medical conditions, including if you:**

- have a disease that affects your muscles and nerves (such as amyotrophic lateral sclerosis [ALS or Lou Gehrig's disease], myasthenia gravis or Lambert-Eaton syndrome). See "What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?"
- have allergies to any botulinum toxin product
- had any side effect from any botulinum toxin product in the past
- have or have had a breathing problem, such as asthma or emphysema
- have or have had swallowing problems
- have or have had bleeding problems
- have plans to have surgery
- had surgery on your face
- have weakness of your forehead muscles, such as trouble raising your eyebrows
- have drooping eyelids
- have any other change in the way your face normally looks
- have symptoms of a urinary tract infection (UTI) and are being treated for urinary incontinence. Symptoms of a urinary tract infection may include pain or burning with urination, frequent urination, or fever.
- have problems emptying your bladder on your own and are being treated for urinary incontinence
- are pregnant or plan to become pregnant. It is not known if **BOTOX** or **BOTOX Cosmetic** can harm your unborn baby.
- are breast-feeding or plan to breastfeed. It is not known if **BOTOX** or **BOTOX Cosmetic** passes into breast milk.

**Tell your doctor about all the medicines you take**, including prescription and nonprescription medicines, vitamins and herbal products. Using **BOTOX** or **BOTOX Cosmetic** with certain other medicines may cause serious side effects. **Do not start any new medicines until you have told your doctor that you have received BOTOX or BOTOX Cosmetic in the past.**

Especially tell your doctor if you:

- have received any other botulinum toxin product in the last four months
- have received injections of botulinum toxin, such as *Myobloc*® (rimabotulinumtoxinB), *Dysport*® (abobotulinumtoxinA), or *Xeomin*® (incobotulinumtoxinA) in the past. Be sure your doctor knows exactly which product you received.
- have recently received an antibiotic by injection
- take muscle relaxants
- take an allergy or cold medicine
- take a sleep medicine
- take anti-platelets (aspirin-like products) and/or anti-coagulants (blood thinners)

**Ask your doctor if you are not sure if your medicine is one that is listed above.**

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist each time you get a new medicine.

#### **How should I take BOTOX or BOTOX Cosmetic?**

- **BOTOX** or **BOTOX Cosmetic** is an injection that your doctor will give you.
- **BOTOX** is injected into your affected muscles, skin, or bladder.
- **BOTOX Cosmetic** is injected into your affected muscles.
- Your doctor may change your dose of **BOTOX** or **BOTOX Cosmetic**, until you and your doctor find the best dose for you.
- **Your doctor will tell you how often you will receive your dose of BOTOX or BOTOX Cosmetic injections.**

#### **What should I avoid while taking BOTOX or BOTOX Cosmetic?**

**BOTOX** and **BOTOX Cosmetic** may cause loss of strength or general muscle weakness, or vision problems within hours to weeks of taking **BOTOX** or **BOTOX Cosmetic**. **If this happens, do not drive a car, operate machinery, or do other dangerous activities.** See "What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?"

#### **What are the possible side effects of BOTOX and BOTOX Cosmetic?**

**BOTOX** and **BOTOX Cosmetic** can cause serious side effects. See "What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?"

#### **Other side effects of BOTOX and BOTOX Cosmetic include:**

- dry mouth
- discomfort or pain at the injection site
- tiredness
- headache
- neck pain
- eye problems: double vision, blurred vision, decreased eyesight, drooping eyelids, swelling of your eyelids, and dry eyes.
- urinary tract infection in people being treated for urinary incontinence
- painful urination in people being treated for urinary incontinence
- inability to empty your bladder on your own and are being treated for urinary incontinence. If you have difficulty fully emptying your bladder after getting **BOTOX**, you may need to use disposable self-catheters to empty your bladder up to a few times each day until your bladder is able to start emptying again.
- allergic reactions. Symptoms of an allergic reaction to **BOTOX** or **BOTOX Cosmetic** may include: itching, rash, red itchy welts, wheezing, asthma symptoms, or dizziness or feeling faint. Tell your doctor or get medical help right away if you are wheezing or have asthma symptoms, or if you become dizzy or faint.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of **BOTOX** and **BOTOX Cosmetic**. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**General information about BOTOX and BOTOX Cosmetic:**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

This Medication Guide summarizes the most important information about **BOTOX** and **BOTOX Cosmetic**. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about **BOTOX** and **BOTOX Cosmetic** that is written for healthcare professionals.

**What are the ingredients in BOTOX and BOTOX Cosmetic?**

Active ingredient: botulinum toxin type A

Inactive ingredients: human albumin and sodium chloride

**Revised: 08/2015**

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by: Allergan Pharmaceuticals Ireland

a subsidiary of: Allergan, Inc.

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*Dysport*® is a registered trademark of Ipsen Biopharm Limited Company.

*Xeomin*® is a registered trademark of Merz Pharma GmbH & Co KGaA.



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*OnabotulinumtoxinA*

***BOTOX***®

***Cosmetic***

for injection

50

Units/vial

ALLERGAN®

Dispense the enclosed Medication Guide to each patient.



OnabotulinumtoxinA

**BOTOX®**

**Cosmetic**

for injection

100

Units/vial

ALLERGAN®

Dispense the enclosed Medication Guide to each patient.





## BOTOX COSMETIC

onabotulinumtoxinA injection, powder, lyophilized, for solution

### Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0023-39 19
Route of Administration	INTRAMUSCULAR	DEA Schedule	

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
botulinum toxin type A (UNII: E211KPY694) (botulinum toxin type A - UNII:E211KPY694)	botulinum toxin type A	50 [USP U]

### Inactive Ingredients



Ingredient Name			Strength	
Albumin Human (UNII: ZIF514RVZR)				
Sodium Chloride (UNII: 451W47IQ8X)				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0023-3919-50	1 in 1 CARTON		
1		1 in 1 VIAL, GLASS; Type 0: Not a Combination Product		
2	NDC:0023-3919-51	1 in 1 CARTON		
2		1 in 1 VIAL, GLASS; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category		Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA		BLA103000	07/15/2008	

BOTOX COSMETIC				
onabotulinumtoxina injection, powder, lyophilized, for solution				
Product Information				
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0023-9232	
Route of Administration	INTRAMUSCULAR	DEA Schedule		
Active Ingredient/Active Moiety				
Ingredient Name			Basis of Strength	Strength
botulinum toxin type A (UNII: E211KPY694) (botulinum toxin type A - UNII:E211KPY694)			botulinum toxin type A	100 [USP'U]
Inactive Ingredients				
Ingredient Name			Strength	
Albumin Human (UNII: ZIF514RVZR)				
Sodium Chloride (UNII: 451W47IQ8X)				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0023-9232-02	1 in 1 CARTON		
1		1 in 1 VIAL, GLASS; Type 0: Not a Combination Product		
2	NDC:0023-9232-01	1 in 1 CARTON		
2		1 in 1 VIAL, GLASS; Type 0: Not a Combination Product		

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA103000	05/20/2008	

**Labeler** - Allergan, Inc. (144796497)

## Establishment

Name	Address	ID/FEI	Business Operations
Allergan Pharmaceuticals Ireland		219682291	MANUFACTURE(0023-3919, 0023-9232)

Revised: 8/2015

Allergan, Inc.